THE CARLAT REPORT PSYCHIATRY

A CME Publication

Subscribe today! Call 866-348-9279

AN UNBIASED MONTHLY COVERING ALL THINGS PSYCHIATRIC

Special Double Issue! Worth 2 CME Credits

Daniel Carlat, MD
Editor-in-Chief

Volume 14, Number 7&8
July/August 2016
www.thecarlatreport.com

IN THIS ISSUE

Focus of the Month:
Medication in Pregnancy

Learning Objectives

After reading these articles you should be able to: **1.** Describe the changes to pregnancy and lactation labeling made by the FDA. **2.** Identify the risks of untreated psychiatric illness to the mother and baby. **3.** Assess the risks and benefits of using psychiatric medications during pregnancy. **4.** Summarize some of the current findings in the literature regarding psychiatric treatment.

What's New with the FDA Labeling for Pregnancy and Lactation?

Talia Puzantian, PharmD, BCPP
Deputy Editor, The Carlat Psychiatry Report

Dr. Puzantian has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

We've been hearing for some time now about the FDA's plans to revise the long-standing categories A, B, C, D, and X designations for risk of using medications in pregnancy. The new rule (referred to as PLLR for Pregnancy and Lactation Labeling Rule) was proposed in 2008, finalized in 2014, and implementation began during the summer of 2015.

Continued on page 2

In Summary

- A new Pregnancy and Lactation Labeling Rule (PLLR) has been implemented by the FDA and replaces the old ABCDX pregnancy categorization.
- Medications will no longer be given letter grades based on pregnancy risk; instead, a narrative will describe available risk data.
- A new section adds information on pregnancy testing, contraception, and infertility risks of drugs.

Q&A with the Expert

How to Evaluate and Treat Mood Disorders in Pregnancy

Vivien Burt, MD, PhD

Founder and co-director at UCLA Women's Life Center, a perinatal outpatient program in Los Angeles, CA.

Dr. Burt discloses that she has been a paid consultant to Otsuka, Sunovion, Lundbeck, and Takeda. Dr. Puzantian has reviewed this article and has found no evidence of bias in this educational activity.

TCPR: Dr. Burt, you've spent much of your career in psychiatry treating women and teaching about reproductive psychiatry. How do you do your evaluation of pregnant or postpartum women who have psychiatric disorders?

Dr. Burt: Typically, when a patient calls to schedule an appointment, she's been referred to us by an obstetrician, reproductive endocrinologist, internist, or psychiatrist. She may already be pregnant or hope to become pregnant or is post-partum and possibly breastfeeding. I spend time speaking with her on the phone to assess her current state of mental health and functioning, particularly her stability and safety. It's now pretty widely recognized that pregnancy does not protect against mental illness, and the postpartum period is certainly a time of very high vulnerability for women, especially if they've had a history of psychiatric

Continued on page 4

What's New with the FDA Labeling for Pregnancy and Lactation?

Continued from page 1

What was wrong with the old system?

The old pregnancy categories appeared, at least superficially, to be pretty useful. If a drug was labeled "A" it was considered completely safe (only 0.7% of medications in U.S. were considered "A"), "B" was pretty safe, "C" was possibly harmful (most medications fell into this category), "D" was probably harmful but still usable if benefits outweighed risks, and finally "X" was positively teratogenic and not to be used ever in pregnancy. In addition to the grades, companies supplied brief descriptions of the risks, but were not required to describe the data in any systematic way.

There were a few problems with the old system. First, the categories were overly simplistic and couldn't adequately describe the potential for negative outcomes. Many would understandably assume that two medications in the same category must have the same level of risk, but this was not true. For example, both lithium and valproate had been classified as category D, yet the risk of cardiac malformation with lithium is roughly 0.05%–0.1% compared to the 8% risk for neural tube defects with valproate. Complicating things even further for women and their providers was the FDA's ruling that valproate would be considered category X for migraines but would remain category D for other indications.

Another critical issue was that categorization didn't differentiate between information based on animal studies and information gleaned from human studies. For example, new medications could earn a benign category B classification even if there was not a single human study showing safety—as long as animal studies showed no fetal risk. And when new data did become available, changes in categorization were not consistent—yet another problem. You might remember that paroxetine (Paxil) was a category C drug, but when several studies suggested a higher risk for cardiac malformations in exposed fetuses, the FDA changed its status to category D. Later, other studies didn't find this increased risk, but the category designation remained the same (see expert interview with Dr. Burt for more on this issue). The old system allowed a newer medication to be considered innocent until proven guilty, but an older medication with decades of safe experience in women would be considered category C just because of some fetal risk shown in animal studies. This was misleading to clinicians. In the end, while the old system was quick and dirty, it turns out it wasn't very clinically meaningful.

How is the new system different?

I. Sections are shuffled

The old labeling included three sections: pregnancy, labor & delivery, and nursing mothers. In the new system, "pregnancy" includes both pregnancy and labor & delivery, the old term "nursing mothers" is replaced with "lactation," and a new, third section is created, called "females and males of reproductive potential." This last section includes information about pregnancy testing, contraception, and effects on fertility.

II. Instead of letter grades, a longer narrative

The new system abolishes letter grades for drugs and instead requires that manufacturers provide narrative descriptions of risks. The information is organized into three subsections: risk summary, clinical considerations, and data. In addition, if a pregnancy exposure registry exists, you will be given the website or other ways to access it. The idea is that you will be able to read about the risks and then draw your own conclusions about whether the risk/benefit ratio justifies prescribing a drug.

How well does this work in practice? Let's take an example of a recently approved psychiatric drug, cariprazine (Vraylar). You can access the package insert at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/204370lbl.pdf. Now compare cariprazine's labeling with the old labeling for another relatively new antipsychotic, lurasidone (Latuda): http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/200603s000lbl.pdf.

Looking at these two package inserts, you'll see that the new system (used for cariprazine, which was approved in 2015) provides much more detailed information and has no letter grade. The lurasidone label gives us a reassuring B grade, but explains this grade with uninformative statements, ie, that we have no data in humans, either in pregnancy or breastfeeding. With cariprazine, we also have only animal data presented, but at least the label provides contact information

Continued on page 3

What's New with the FDA Labeling for Pregnancy and Lactation?

Continued from page 2

for the registry, which over time will be populated with human data. The cariprazine label also adds useful information about the background risk for malformation and the drug class risks.

Since cariprazine and lurasidone are still relatively new drugs, their current data are limited, but eventually the narrative will include a wealth of details, such as risks associated with underlying illness, necessary dosage adjustments in pregnancy, and effects on labor and delivery.

The old letter grade had the benefit of providing a quick and dirty summary, but as we are learning more about drugs in pregnancy, such a shorthand is no longer feasible. That's unfortunate, because it means we have to slog through narratives that will become longer and longer over time. Luckily, there are publications such as *TCPR* and others whose mission in life is to synthesize this data for you.

Another component of the new PLLR is a statement about background risk of adverse pregnancy outcomes: eg, "The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–20%, respectively."

When does the new system actually begin?

The new system is already in place for all medications approved after June of 2015. For meds that were approved between 2001 and 2015, companies have until 2020 to create the revisions. Finally, for meds approved before 2001, don't hold your breath—the FDA recommends, but does not require, manufacturers to provide new data for these older medications.

TCPR VERDICT: The new labeling has received rave reviews from heavyweight organizations such as The American Academy of Pediatrics and the American College of Obstetrics and Gynecology. Overall, we think this is a step in the right direction, but the longer narratives will be challenging for busy prescribers.

❖ ❖ ❖

Characteristics of Old vs. New FDA Pregnancy/Lactation Labeling

	Old FDA Labeling	New FDA Labeling
Organization of Sections	1. Pregnancy 2. Labor & delivery 3. Nursing mothers	1. Pregnancy (includes labor & delivery) 2. Lactation (new term for "nursing mothers") 3. Females and males of reproductive potential
How Pregnancy Risk Information Is Imparted	1. Categories A, B, C, D, X 2. Narrative with subsections: • Teratogenic effects • Non-teratogenic effects	1. No categories 2. Narrative with subsections: • Pregnancy exposure registry • Risk summary • Clinical considerations • Data
How Lactation Risk Information Is Imparted	Narrative providing animal or human data	Narrative with subsections: • Risk summary • Clinical considerations
How Reproductive Information Is Imparted	Was not addressed	If applicable, narrative describing if pregnancy testing or contraception required and effects on fertility

Burt Interview
Continued from page 1

illness.

TCPR: What if a patient does not seem stable or safe?

Dr. Burt: If she appears to be unstable or unable to function, I will have her seek emergency psychiatric intervention, usually by going to an emergency room, and will not have her wait for an outpatient appointment.

TCPR: And if she seems stable, how do you proceed?

Dr. Burt: For women who are stable enough to wait for an appointment, I send them a detailed questionnaire so that I have a head start before the initial consultation, which is generally a 90-minute appointment. Some patients find it useful to consolidate their history in a way they've actually never done before. I have them describe everything from current symptoms, emotional state, and behavior functioning, to details about past psychiatric history; current health providers; current and past medications, both psychiatric and non-psychiatric, including over-the-counter and alternative agents; substance and alcohol abuse or use now and in the past; medical history; obstetrical history; and of course social and development history. Also, there is the well-validated Edinburgh Postnatal Depression Scale, a 10-item screening instrument widely used to screen for depression both in pregnancy and postpartum which patients can take themselves (Cox JL, *Br J Psychiatry* 1987;150:782–786).

"It's now pretty widely recognized that pregnancy does not protect against mental illness, and the postpartum period is certainly a time of very high vulnerability for women, especially if they've had a history of psychiatric illness."

Vivien Burt, MD, PhD

TCPR: So if during your screening process you determine that a patient is high risk, what's your best practice in terms of working with the referring doctor?

Dr. Burt: One of the things I do is provide patients and their health care providers (with the patient's consent) a written copy of the final consultative report, which summarizes the patient's clinical status as well as my recommendations. I also include relevant citations from the current literature that support my treatment recommendations. Referring clinicians are often worried about incurring liability for making such recommendations, so I feel that this is the best approach to address any of their medical/legal liability concerns. An important part of that report is a written case formulation. It puts together my understanding of the patient psychodynamically in terms of her psychiatric diagnosis so that my treatment recommendations reflect my best understanding of what will work for that particular patient.

TCPR: And then do you take over the treatment?

Dr. Burt: It depends on the situation. Some referring clinicians prefer that I follow and treat their patients through pregnancy and postpartum, and then refer them back after six to 12 months postpartum once everything is stable and the patient and her baby are doing well. Other times, we just provide that one-time consultation. Many clinicians feel very comfortable following our recommendations, and we are happy to provide clarification or additional consultations as needed.

TCPR: What's your thought process like as you evaluate whether women wanting to become pregnant should be on antidepressants?

Dr. Burt: When I see patients who want to know the risks of antidepressants in pregnancy, I always start by addressing possible risks and benefits of *not* using antidepressants in pregnancy. The main risk, of course, is relapse. For example, let's say I'm seeing a patient who is in her 20s or her early 30s. She's been on antidepressants for a long time, and she's stable. It's reasonable for her to defer pregnancy for a while so that we can taper her off her medication, and we'll follow her, say, for six months or so. If she continues to be fine off the antidepressant, then she can become pregnant without exposing the fetus to medication, which is the best approach, other things being equal. But if she relapses, I'll generally recommend restarting the medication to keep her stable.

TCPR: What about the woman who is older and feels like the "clock is ticking" on her fertility? Do you make different recommendations?

Dr. Burt: Absolutely. If a patient is in her late 30s or maybe her early 40s, we don't have as much time to wait to see if she's stable off medication. Continuing the antidepressant she's been on may be the wiser plan. No two cases are the same, and the best treatment approach is always individualized for a patient's specific circumstance.

TCPR: That brings us to the crux of the matter, which is the risks of being on antidepressants during pregnancy. There are plenty of studies, and it can get pretty confusing. Can you summarize where we are with antidepressants right now and what are the things we need to think about?

Dr. Burt: Antidepressants in general may be associated with an increased risk for somewhat shorter gestation—about 3 days or so, certainly less than a week, which is generally not clinically significant. With regard to birth weight, antidepressants may be associated with a reduction in birth weight of about 75 grams, which is about 2–1/2 ounces or so, which, again, is generally not of clinical significance.

Continued on page 5

Burt Interview
Continued from page 4

TCPR: What about SSRIs specifically?

Dr. Burt: As a group, serotonergic agents—whether we're talking about SSRIs or SNRIs—are not considered major teratogens, certainly nowhere close to drugs like Accutane or thalidomide. If you do a literature search, individual articles suggest specific malformations with one SSRI or another. The problem is that most of these studies have flaws because ethically you can't do the gold standard studies that would give us definitive answers. Specifically, we can't do randomized controlled trials in which we assign pregnant women randomly to antidepressants vs. placebo. The potential risks to the fetus are too great.

TCPR: So what's the bottom line on SSRIs and SNRIs?

Dr. Burt: What should be noted, of course, is that any pregnancy carries somewhere between a 3% and 5% risk for major congenital anomalies, and that maternal stress and depression itself during pregnancy have also been associated with adverse reproductive outcomes. The bottom line is that these medications do not appear to increase the risk for major congenital anomalies, with the exception of paroxetine, which does have a number of studies suggesting an increased risk for cardiac malformations, particularly right ventricular defects. But even here, it should be noted that there is some controversy even about whether paroxetine is a problem; because there are enough articles that concern us, we tend to not use it as a first-line agent. The other issue readers may be aware of is persistent pulmonary hypertension (PPHN). This is a serious condition that can be lethal, and some years ago there were some data associating it with SSRI exposure. But a number of more recent studies have called this into question, suggesting that other issues like cesarean sections may be responsible rather than SSRI exposure. In 2011, the FDA issued a public safety announcement advising health care professionals not to alter their current clinical practice of treating depression during pregnancy. They stated, and I'll quote this, "It is premature to reach any conclusion about a possible link between SSRI use in pregnancy and PPHN."

TCPR: Aside from major abnormalities, are there any other concerns about antenatal antidepressant exposure?

Dr. Burt: One issue that does appear to be associated with antenatal antidepressant exposure is that of neonatal adaptive difficulties occurring just after delivery. This has various names, but one that has been gaining traction is PNAS (perinatal neonatal adaptation syndrome). It occurs in about 30% of deliveries, so I've encountered this with my patients. The symptoms include jitteriness, decreased muscle tone, grunting (which is suggestive of respiratory distress), and difficulty sucking. These adverse effects tend to be quite mild and generally very transient. In most cases, infants recover quite quickly within hours—and certainly within days—and they do well subsequently. In general, I always suggest that new mothers on antidepressants in pregnancy and their neonates remain in the hospital for 48 hours post-delivery to ensure that the babies are healthy and progressing well.

TCPR: There continues to be some confusion around whether antidepressants should be tapered prior to delivery to minimize these issues.

Dr. Burt: In my opinion, it makes no sense to taper off a required serotonergic antidepressant prior to delivery. This is when a mother is entering her most vulnerable time psychiatrically—the postpartum period—when she not only has the responsibility for looking after herself, but also a baby that is dependent on her. We always use what I call the minimal effective dose, and those two words "minimal" and "effective" are equal. You want to minimize the dose, yes; but what's the point of using a dose that's so low that it's not effective? Now you have exposure without achieving the desired effect.

TCPR: What are the data about what happens when a woman is on an antidepressant, becomes pregnant, and goes off it?

Dr. Burt: You may be aware of the three-site naturalistic prospective study from 2006 in which we found that recurrence risk was significantly higher with a 68% relapse rate for women who discontinued antidepressant around the time of conception compared to 26% in those who maintained antidepressant treatment. And recurrences emerged rapidly—50% in the first trimester and 90% by the end of the second trimester. So that's important information (Cohen LS et al, *JAMA* 2006;295(5):499–507). The conclusion is that women are at risk of relapse in many cases, and that pregnancy per se is not going to prevent relapse. And especially for the patient who has shown us that, in the past, every time she goes off her medication she relapses, you may want to continue the medication.

TCPR: What are your thoughts on treating anxiety or insomnia during pregnancy in women who've never had a psychiatric history?

Dr. Burt: First-line treatments include interventions like cognitive behavioral therapy (CBT), reducing psychosocial stressors, and eliminating stimulants such as caffeine and nicotine. You don't want to smoke anyway during pregnancy for obvious reasons. Sometimes couples therapy is indicated. For insomnia specifically, you want to ensure sleep hygiene as a first-line treatment. You want to suggest decreasing fluids prior to bedtime, massage, and stretching. CBT for insomnia has been manualized and endorsed by NIH and works well for motivated patients.

TCPR: So medications for anxiety and insomnia are further down the list of options?

Dr. Burt: Yes. Serotonergic antidepressants can sometimes be reasonable options for symptoms that are so severe that they

Continued on page 10

Q&A With the Expert

Assessing Illness and Medication Treatment in the Perinatal Period

Simone Vigod, MD

Assistant professor at the University of Toronto and Institute of Health Policy in Toronto, Canada.

Dr. Vigod has disclosed that she has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

TCPR: Dr. Vigod, we know that it's best to avoid medications if we can in pregnant women. But that's more easily said than done. What's your approach?

Dr. Vigod: I start by assessing the severity of the symptoms and the impact on function. Women usually fall into two categories: those who are not on medication and have become symptomatic, and those who have been taking medication, who are perhaps in remission, and are unsure about going off medication during pregnancy.

TCPR: For the women who are symptomatic and not on medication, what are the options?

Dr. Vigod: You can leave them untreated; you could treat them with a nonpharmacological option and/or you could treat them with a pharmacological option. For women who have mild symptoms, the hope is that you can treat with psychosocial interventions that might include exercise, stress reduction, increased social support from their social network and/or peer support, or psychological therapies. With women with more moderate symptomatology, the question is, can this be adequately treated with psychological therapies? There are barriers to psychological therapies: time off from work, school, or current parenting responsibilities that can involve time, coverage, and monetary challenges. Another consideration is if the woman either doesn't respond to psychotherapy or is taking too long to respond. Psychotherapy is usually a 12- or 16-week trial, and that potentially means a woman doesn't get better for 16 weeks, during which time the fetus is exposed to untreated depression and anxiety.

TCPR: What are the effects of untreated depression and anxiety on the baby?

Dr. Vigod: Untreated anxiety or depression in pregnancy is not benign. It can affect the developing fetus directly. Some research suggests that prenatal stress can increase cortisol levels, which can affect the fetus in various ways (Gover V et al, *Neurosci Biobehav Rev* 2010 35(1):17–22). We also know that untreated anxiety/depression in pregnancy is associated with smaller babies, babies born more preterm, and infants that are more irritable. There's also evidence to suggest that untreated anxiety/depression in pregnancy might affect the infant's developmental outcomes—though it's very hard to disentangle whether this is due to prenatal stress or anxiety in the mother after the child is born. Untreated anxiety/depression in pregnancy can also affect a fetus indirectly because such women may be more likely to smoke, use alcohol, sleep less well, eat less well, or potentially not have the same level of antenatal care. Untreated anxiety and depression in pregnancy is also the strongest risk factor for postpartum depression and anxiety, which we know clearly have an impact on maternal infant attachment, and can even lead to delays in language and motor development as well as child internalizing and externalizing disorders.

TCPR: And what about the impact of untreated illness on the mother?

Dr. Vigod: For the mother, the longer you leave the depressive or anxiety disorder untreated, the harder it is to treat, and the more likely it is to become chronic. And so the greatest risk factor for postpartum depression and anxiety is untreated antenatal depression and anxiety.

"Untreated anxiety or depression in pregnancy is not benign… [it] is associated with smaller babies, babies born more preterm, and infants that are more irritable."

Simone Vigod, MD

TCPR: So it sounds like there are many really good reasons to treat depression and anxiety in pregnancy. How do you present the risks to new mothers without needlessly alarming them?

Dr. Vigod: In my opinion, we should have a high threshold for medication use in pregnancy, but we should use them when we have to use them. With that said, when talking to a new or potential mother, you want to present an absolute number or absolute risk when possible—because relative risks can be deceiving. For example, if there is a 0.5% risk of an abnormality, I will say that there is a 5 in 1,000 risk of this thing happening—but will add that this also means there is a 995 out of 1,000 chance of it *not* occurring. If you can present visuals, that's very helpful. For example, suppose you have an abnormality that occurs in 5 of 1,000 births at baseline, and occurs in 8 of 1,000 births with exposure to a medication. In relative terms, this is a 60% increased risk (3 extra events divided by 5 events at baseline), which can sound pretty terrifying. But if you have a picture of 1,000 faces and you color in 5 for baseline risk and an extra 3 for the increased risk with medication, you can see that's actually really small. Some women may not want to tolerate even that increased risk, and that's fine, but you want to make sure they have an accurate view of the amount of risk.

Continued on page 7

Vigod Interview

Continued from page 6

TCPR: Let's talk about women who may already be taking medication. What do you do if a medication is so new that we don't have any kind of study data to extrapolate from?

Dr. Vigod: First of all, we would try not to use something so new. But if a woman is coming to me on one of these newer medications, she's tried three older medications, she has a history of suicidality and it took her five years to really get better, the risk of taking her off that medication and switching her to something else would be awfully high. So I would educate her about the fact that we don't have data, but that nevertheless we have to weigh that against the risk of coming off a medication that has been so helpful.

TCPR: Can we rely on animal data?

Dr. Vigod: Not necessarily. Thalidomide was not teratogenic in rats or mice, and there are examples where drugs were teratogenic in animals but not in humans. Most human teratogens have been discovered in post-marketing drug surveillance—either a physician doing a case report or large epidemiological studies.

TCPR: Just to shift gears now, you recently published a study on the risks of antipsychotics in pregnancy. What did you find?

Dr. Vigod: So there have already been a few studies on antipsychotics in pregnancy, and the data thus far are pretty reassuring. There were some concerns about metabolic issues like gestational diabetes and hypertension. In our study, we used a special matching method that approximates the quality of data you might get in a randomized controlled trial (Vigod SN et al, *BMJ* 2015;350:h2298. doi:10.1136/bmj.h2298). We found almost no differences between groups in terms of outcomes for mom or for baby after the matching. However, women in both groups (the antipsychotic group *and* the matched group) had negative outcome rates that were much higher than one would expect in the general population. This means that antipsychotic users are likely to be a high-risk population around the time of pregnancy, but that the risk for adverse outcomes shouldn't be blamed on the drug.

TCPR: Is your consideration the same when the indication is a mood disorder versus a psychotic disorder?

Dr. Vigod: I think that the answer is yes for severe disorders such as schizophrenia or bipolar disorder, because it seems fairly clear that women with these conditions will relapse when medication is discontinued. Antipsychotics are now being used more and more for major depressive disorder, usually as adjunctive therapy. In depression, I would always say that monotherapy is better. If we can avoid it, we probably should, since you never know how two drugs mix together. But I guess it all comes back to my thesis, which is we should be treating people with what they need.

TCPR: Can you tell us what's coming down the pike in perinatal psychiatry?

Dr. Vigod: Sure. Our team created an online patient decision aid to help women navigate decisions around antidepressant use in pregnancy. We are now finishing a pilot randomized controlled trial where we compared use of this decision aid to a PDF resource sheet. Our hope would be that if we can show it reduces women's decision-making difficulty, then this would be an online intervention that we can update centrally as often as we need with the appropriate evidence and can be potentially

Continued on page 12

Developmental Effects of Prenatal Selective Serotonin Reuptake Inhibitor Exposure in Perspective: Are We Comparing Apples to Apples?

(Oberlander TF and Vigod SN, *J Am Acad Child Adolesc Psychiatry* 2016;55(5):351–352).

Dr. Vigod recently co-authored an editorial in response to a cohort study in Finland that found a 1.8-fold increased incidence of depression, but not autism or ADHD, by early adolescence among offspring exposed to SSRIs in the prenatal period. Here's her summary of that editorial.

There were two main points that we wanted to get across. Point one is that when we're looking at outcomes for SSRIs, we want to be comparing apples to apples to isolate the effect of the SSRI. The authors attempted to do this as much as possible, but there were unmeasurable factors that may have been more highly associated with SSRI use. For example, a big issue is that depression is a heritable disorder. Without knowing what the genetic basis is of a given woman who is also taking an SSRI, it is hard to know what her child's risk of depression is going to be. If a woman is more likely to take an SSRI during pregnancy if she has a bona fide genetic depression, then wouldn't her child also have an increased risk of having depression compared to a woman who has less severe depression? And then also, when you're looking at adolescents, you have to consider all the stuff we know about the environment of postnatal depression and anxiety. Someone who is depressed enough in pregnancy to take a medication—and depression is a chronic and recurrent disorder—what does that mean about that child's early childhood environment putting them at risk for depression?

Point two is around the fact that there are many different possible maternal and child development outcomes, and the idea that we might want to shift away from a research model where SSRIs are either "good" or "bad." If you look at some of Dr. Oberlander's work, you can see how SSRIs may be protective for some outcomes in some environmental circumstances but not others (Hanley GE and Oberlander TF, *Birth Defects Res A Clin Mol Teratol* 2012;94(8):651–659). So the story about SSRIs may be more complex than some have previously considered.

Research Updates IN PSYCHIATRY

Section Editor, Bret A. Moore, Psy.D, ABPP

Dr. Moore has disclosed that he has no relevant financial or other interests in any commercial companies pertaining to this educational activity.

ANTIPSYCHOTICS

Metoclopramide Helps Clozapine-Related Drooling (Kreinin A et al, *J Clin Psychopharmacol* 2016;36:200–205)

Excessive salivation is a common and troubling adverse effect of clozapine therapy, occurring in about 30% of patients. It's often worse at night, and waking up with a wet pillow is not a good way for patients to start their day. There are various things to try for this problem, including anticholinergics such as Artane and Cogentin, alpha adrenergics like clonidine and guanfacine, and sublingual drops such as atropine or pilocarpine. None of them work consistently, and they all have their potential side effects. Recently, Israeli researchers evaluated another potential treatment, metoclopramide (Reglan), which is a drug for nausea and other gastrointestinal problems. Since metoclopramide commonly causes dry mouth, the authors of this paper reasoned that it might work for clozapine-induced hypersalivation.

Over a two-year period, 58 inpatients treated with clozapine and experiencing hypersalivation were randomized to receive metoclopramide (30 patients) or placebo (28 patients). Both groups were tracked over 3 weeks. During the first week, the metoclopramide group received 10 mg at bedtime. If there was no response, an additional 10 mg was added in the morning during the second week and another 10 mg in the afternoon during the third week. Researchers used a variety of subjective and objective measures to assess improvement.

At the end of the study, 66.7% (N=20) of those who received metoclopramide showed improvement or outright disappearance of drooling, significantly more than the 28.6% (N=8) of those who took placebo (p = 0.031). No patients in the metoclopramide group reported an adverse reaction.

TCPR's Take: Drooling can be a deal breaker for patients taking clozapine. While this randomized controlled trial is of short duration and based on a relatively small sample, the results support the use of metoclopramide for this distressing side effect. There is one note of caution, however: Metoclopramide is a dopamine antagonist and can cause tardive dyskinesia and other movement disorders. So monitor patients closely if you choose to add metoclopramide to the mix.

COMPULSIVE BEHAVIOR

N-acetylcysteine Shows Promise for Skin-Picking Disorder (Grant J et al, *JAMA Psychiatry*, 2016;73:490–496)

Excoriation, or what's often referred to as skin-picking disorder (SPD), is a distressing and disfiguring behavior that affects up to 5% of people, occurring more commonly in women. Various lines of evidence imply that this compulsive behavior may be related to reduced levels of glutamate in the nucleus accumbens. N-acetylcysteine is an antioxidant that increases glutamate, and studies have shown that it is effective for excoriation's sister disorder, trichotillomania (hair pulling). These data prompted investigators to try N-acetylcysteine in the treatment of SPD.

Over a 12-week period, 66 adult SPD patients from two Midwestern university-based clinics were randomized in a double-blind study to receive N-acetylcysteine (n=35) or placebo (n=31). The N-acetylcysteine group received 1,200 mg/day to start, increased to 2,400 mg/day by week three, and 3,000 mg/day by week six. An excoriation-specific version of the Yale-Brown Obsessive Compulsive Scale (NE-YBOCS) was used to assess picking symptoms over the three months. Researchers also used the Clinical Global Impression-Severity scale and other self-report, subjective measures.

The N-acetylcysteine seemed to work. Baseline NE-YBOCS scores dropped from 18.9 to 11.5 for the treatment group by the end of 12 weeks. During the same time period, the placebo scores shifted from 17.9 to 14.1. Subjective self-reports by the patients were also strong. Of the 53 patients who completed the study, 47% of the N-acetylcysteine group felt they were "much" or "very much" improved compared to only 19% of the placebo group. No significant adverse events were noted.

TCPR's Take: The study was small, but given the benign side effect profile of N-acetylcysteine, it's worth trying for patients with SPD.

SUICIDE

Buprenorphine for Suicidality? Maybe (Yovell Y et al, *Am J Psychiatry* 2016;173:491–498)

When patients become severely suicidal, we have few good treatment options. These include close monitoring (often in a locked unit), intensive psychotherapy, antidepressants (which, while effective, take weeks to work), a variety of medications to treat symptoms such as agitation and insomnia, and more recently, the experimental treatment ketamine (which requires repeated infusions under medical supervision). In addition, lithium reduces suicidality in bipolar disorder, and clozapine does so in schizophrenia—but both are long-term treatments.

Continued on page 9

Research Updates
Continued from page 8

Recognizing the need for more options, Israeli researchers studied the use of very low doses of buprenorphine in suicidal patients. Patients with suicidal ideation were recruited from four medical centers. The participants were severely suicidal, with an average score of 19.7 on the Beck Scale for Suicidal Ideation; 64% of them had made at least one suicide attempt. They were randomly assigned to either buprenorphine (n = 40) or placebo (n = 22). Buprenorphine was started at 0.1 mg once or twice a day and gradually titrated up to a max dose of 0.8 mg/day (average dose was 0.44 mg/day). No changes to the regular psychiatric treatment were made. Most of the patients' from both groups were on medication, including over 70% who were taking antidepressants. The primary outcome measure was change from baseline on the Beck scale, which was assessed weekly for 4 weeks.

The buprenorphine seemed to work. After 2 weeks, suicide severity dropped by an average of 4.3 points more in the buprenorphine group than the placebo group, and after 4 weeks, the difference was 7.1 points; both values were statistically significant. Adverse events occurred in 77.2% of the buprenorphine patients, and in 54.8% of the placebo patients. The most common buprenorphine-related side effects were fatigue (49.1%), nausea (36.8%), and constipation (26.3%). After 4 weeks, the medication was stopped without a taper, and no patients reported any withdrawal symptoms over the ensuing week, nor was there any exacerbation in suicidality.

TCPR's Take: This was a small study and of short duration, but the results were encouraging. A brief course of ultra-low-dose buprenorphine may be worth trying in your patients with severe suicidal ideation. Keeping the dose low and limiting the duration to around 4 weeks are likely crucial for preventing opioid addiction in these patients.

ANTIDEPRESSANTS

Citalopram Safety Warning Has Serious Consequences for VA Patients (Rector T et al, *Am J Psychiatry*, 2016; ahead of publication)

In the summer of 2011, the Food and Drug Administration (FDA) reported that post-marketing surveillance showed that patients taking greater than 40 mg/day of citalopram were at greater risk of QT prolongation. The agency advised doctors not to prescribe doses higher than 40 mg/day, and no higher than 20 mg/day in the elderly. Shortly thereafter, the Department of Veterans Affairs (VA) alerted its providers to this warning. VA researchers recently published a study detailing the results of this warning on patients.

A search of the VA national electronic health records found that in August 2011, shortly after the FDA issued the warning, 35,848 patients had a prescription higher than 40 mg/day of citalopram, with an average dose of 64 mg/day. Although VA clinicians were not required to decrease doses after the warning, many did. Within six months of the warning, 60% of the high-dose patients had been prescribed doses of 40 mg/day or less. The researchers compared rates of hospitalizations and mortality in patients whose dose was decreased vs. those who continued on high-dose citalopram.

Hospitalization or death for any reason was 2.5 times greater in the reduced-dose group vs. the maintained-dose group. Depression-related hospitalizations were also higher in the reduced-dose group, as was self-injurious behavior. Interestingly, reducing the dose did not do anything obvious to prevent arrhythmia—there was no drop in hospitalization for cardiac arrhythmias. The researchers concluded that the FDA warning did more harm than good.

TCPR's Take: If you have patients who are doing well on high-dose citalopram, don't reduce the dose just based on the FDA warning. Instead, check an EKG, and if there is a prolonged QT interval, consult with a cardiologist to determine whether the risk of an arrhythmia is high enough to justify slashing the dose of an antidepressant. Judging by the results of this study, you may ultimately decide to stay the course.

❖ ❖ ❖

Burt Interview

Continued from page 5

suggest generalized anxiety disorder or panic disorder which might be causing the insomnia. And sometimes even occasional, intermittent, low doses of benzodiazepines, especially after the first trimester, do not appear to be harmful to the fetus. But the use of benzodiazepines is still somewhat controversial, with older research suggesting a risk of oral cleft, although more recent data do not appear to support that conclusion. But with regard to other pharmacologic approaches, although antihistamines (like most other sleep aid medications) can have a rebound effect, sometimes obstetricians prescribe Unisom with doxylamine. In fact, something called Diclegis, which is a delayed-release tablet containing doxylamine and pyridoxine, has been FDA approved to treat morning sickness. Obstetricians also frequently prescribe zolpidem for intractable insomnia in pregnancy. Although human data are limited for that, animal studies as well as reports from the FDA adverse event risk monitoring system have found no increased risk for congenital malformations with this agent.

TCPR: In terms of adjusting medications during pregnancy, are there effects that the pregnancy itself may have on medications?

Dr. Burt: There are significant changes in both estrogen, progesterone, and other hormones, all of which are meant to sustain a pregnancy and also ultimately prepare for the delivery and eventually for breastfeeding. For example, estrogen levels rise quickly and steadily throughout pregnancy, and estrogen enhances the clearance of lamotrigine by inducing p450 liver enzymes involved in this metabolism. So as a result, maternal serum lamotrigine concentration frequently declines as the pregnancy progresses. In fact, over the course of pregnancy, lamotrigine levels may dip by as much as 50%, and therefore some women may experience clinical worsening of their bipolar symptoms. Lamotrigine serum concentrations tend to return to pre-pregnancy values within 3–4 weeks postpartum. If this does occur, serum levels may cause postpartum toxicity, and that can be manifested by symptoms including ataxia, nausea, dizziness, blurred vision as early as 3 days after delivery if the dose isn't decreased. In other words, pregnant women taking lamotrigine for bipolar disorder may relapse because of declining serum levels and may become toxic after delivery.

TCPR: Speaking of bipolar disorder, what is the latest on the use of lithium in pregnancy?

Dr. Burt: Lithium is still the gold standard for bipolar disorder in pregnancy, in my opinion. The absolute risk for cardiac defects in exposed fetuses is far less than the risk of bipolar decompensation with inadequate treatment. Having said this, there are a number of caveats to think about when using lithium in pregnancy. Obviously, fetal development really has to be monitored carefully and in general is a part of routine obstetrical management—things like the nuchal translucency test measured at 12 weeks' gestation, and a high-level structural ultrasound at weeks 18–20, are very good ways to assess and screen for normal fetal development. A fetal echocardiogram is also sometimes done when indicated.

TCPR: What should we know about how pregnancy might affect lithium levels?

Dr. Burt: Over the course of pregnancy, extracellular fluid levels rise and renal clearance of lithium increases, so it's important to ensure that lithium levels remain therapeutic—about 0.8 to 1.2 mEq/L generally. Levels should be checked regularly once a month during the first half of pregnancy and more often during the latter half of pregnancy. Situations that tend to increase lithium levels should be avoided, and these would include dehydration, the use of NSAIDs or diuretics, calcium channel blockers, and ACE inhibitors. At times, an obstetrician may encourage a sodium-restricted diet to manage preeclampsia and which can inadvertently increase a patient's lithium levels.

TCPR: And how might lithium levels be affected during delivery and shortly thereafter?

Dr. Burt: Maternal lithium toxicity is possible in cases of acute loss of fluids at delivery, or hyperemesis gravidarum or preeclampsia. Because of these potential issues, some have suggested that lithium should be withheld during the first one or two days before a planned delivery or at the start of labor, but in our clinic we tend not to do this and rely on careful surveillance throughout labor and delivery to guard against maternal lithium toxicity. Preconception doses of lithium should be reinstated once the mother is medically stabilized following delivery. Because bipolar women are at high risk for serious bipolar illness during the postpartum, clinical status should be carefully monitored, and lithium dosing adjusted accordingly.

TCPR: Thank you for your time, Dr. Burt.

❖ ❖ ❖

CME Post-Test

This CME test is only available to active subscribers and it must be taken by August 31, 2017. If your subscription expires before that date, you will not have access to the test until your subscription is renewed. To earn CME or CE credit, you must read the articles and then take the post-test at www.TheCarlatReport.com. You must answer at least four questions correctly to earn credit. You will be given two attempts to pass the test. As a subscriber to *TCPR*, you already have a username and password to log onto www.TheCarlatReport.com. To obtain your username and password, please email info@thecarlatreport.com or call 978-499-0583.

The Carlat CME Institute is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians. Carlat CME Institute is also approved by the American Psychological Association to sponsor continuing education for psychologists. Carlat CME Institute maintains responsibility for this program and its content. Carlat CME Institute designates this enduring material educational activity for a maximum of two (2) AMA PRA Category 1 Credits™ or 2 CE credits for psychologists. Physicians or psychologists should claim credit commensurate only with the extent of their participation in the activity.

For those seeking ABPN Self-Assessment (MOC) credit, a pre- and post-test must be taken online at http://thecarlatcmeinstitute.com/self-assessment/

Below are the questions for this month's CME/CE post-test. This page is intended as a study guide. Please complete the test online at www.TheCarlatReport.com. Note: Learning Objectives are listed on page 1.

1. Which of the following was one of the problems with the previously used ABCDX system for pregnancy labeling? (Learning Objective #1)
   - [ ] a. It was overly simplistic
   - [ ] b. It was based solely on animal data
   - [ ] c. It was not updated when new information became available
   - [ ] d. It assigned the same classification to all medications within a class

2. Antidepressants have been shown to shorten gestation by the following time period. (LO #3)
   - [ ] a. 0 days
   - [ ] b. 3 days
   - [ ] c. 7 days
   - [ ] d. 14 days

3. Women treated with antipsychotics during pregnancy may have a higher risk for negative pregnancy and neonatal outcomes that are independent of the antipsychotic's effects. (LO #2)
   - [ ] a. True [ ] b. False

4. In a recent study of buprenorphine in suicidal patients, which was the most common buprenorphine-related side effect? (LO #4)
   - [ ] a. Constipation
   - [ ] b. Dry mouth
   - [ ] c. Fatigue
   - [ ] d. Blurry vision

5. In the Finnish study that found an increased risk of developing depression in offspring exposed to SSRIs in utero, a significant confounder may have been the role of genetics. (LO #3)
   - [ ] a. True [ ] b. False

6. The new Pregnancy and Lactation Labeling Rule provides a statement about background risk of major defects. In the U.S., this risk is estimated to be: (LO #1)
   - [ ] a. 1%–2%
   - [ ] b. 2%–4%
   - [ ] c. 6%–10%
   - [ ] d. 15%–20%

7. Which of the following is a risk of untreated depression or anxiety in a pregnant woman? (LO #2)
   - [ ] a. Decreased antenatal care
   - [ ] b. Increased smoking or alcohol use
   - [ ] c. Poor nutrition
   - [ ] d. All of the above

8. Perinatal psychiatrists generally recommend discontinuing antidepressants prior to delivery to minimize negative outcomes. (LO #2)
   - [ ] a. True [ ] b. False

PLEASE NOTE: WE CAN AWARD CME CREDIT ONLY TO PAID SUBSCRIBERS

This Month's Focus:
Medication in Pregnancy

Next month in *The Carlat Psychiatry Report:* Pain Management

Special Double Issue!
Worth 2 CME Credits

THE CARLAT REPORT: PSYCHIATRY

P.O. Box 626
Newburyport, MA 01950

PRSRT STD
US Postage
PAID
Nashville, TN
Permit 989

Vigod Interview
Continued from page 7

scaled back for use in clinical practice.

TCPR: Any other research we should be aware of?

Dr. Vigod: We are studying the feasibility of a brain stimulation treatment for depression in pregnant women—transcranial direct current stimulation (tDCS). Women receive 30 minutes of treatment, 5 days a week over 3 weeks (15 sessions). We are doing it at the hospital to allow for continuous fetal monitoring around the time of the stimulation. It's going to take some time before we finish our pilot study and do a much larger study, but the hope would be to provide another safe and effective treatment option for depression in pregnancy.

TCPR: That is exciting. Thank you for your time, Dr. Vigod.

❖ ❖ ❖